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Morphometry of superficial glomeruli in acute hypertension in the rat

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Morphometry of superficial glomeruli in acute hypertension in the rat. Pressor doses of angiotensin II (AII) were infused intravenously in Munich-Wistar rats to study the effects of acute hypertension on the structural components of the superficial renal corpuscles and urinary protein excretion. AII administration raises arterial blood pressure by 38% and increases 13-fold the normal rate of urinary excretion of proteins that contain albumin and IgG. Morphometric analysis of the quantitative characteristics of the glomerular capillaries reveals a 24% increase in the mean cross-sectional area of the capillary profiles and a 33% expansion of the capillary luminal volume. The amount of extracellular material present in the mesangium is also increased by 76%. The surface area of basement membrane available for ultrafiltration remains constant. However, the length density and the total length of the filtration slit diaphragms are reduced by 35 and 24%, respectively. Thus, the major findings of this investigation are as follows: *(1)* The presence of IgG in the urine suggests a size defect in the glomerular filter with AII-induced hypertension; *(2)* the dilatation of capillary loops may result in mechanical stretching of the basement membrane, altering the size-selective properties of the glomerular filter in acute hypertension; and *(3)* the reduced pore area of the filtration slit diaphragms implies a lower hydraulic conductivity of the glomerular filter that may be responsible for the decreased glomerular capillary ultrafiltration coefficient present in this model of hypertension.

Morphométrie des glomérules superficiels lors d'une hypertension aiguë chez le rat. Des doses pressives d'angiotensine II (AII) ont été perfusées par voie intraveineuse chez des rats Munich-Wistar pour étudier les effets d'une hypertension aiguë sur les constituants structuraux des corpuscules rénaux superficiels et sur l'excrétion urinaire de protéines. L'administration d'AII élève la pression artérielle de 38% et augmente 13-fois le débit normal d'excrétion urinaire de protéines contenant de l'albumine et de l'IgG. L'analyse morphométrique des caractéristiques quantitatives des capillaries glomérulaires révèle une augmentation de 24% de la surface de section transversale moyenne des capillaries et une expansion de 33% du volume luminal capillaire. La quantité de matériau extracellulaire présent dans le mésangium est également augmentée de 76%. La surface de la membrane basale disponible pour l'ultrafiltration reste inchangée. Cependant, la densité en longueur et la longueur totale des slit-diaphragmes de filtration sont réduites de 35 et de 24%, respectivement. Ainsi, les résultats principaux de cette étude sont les suivants: *(1)* La présence d'IgG dans les urines suggère un défaut sur la taille dans le filtre glomérulaire lors de l'hypertension induite par l'AII; *(2)* la dilatation des anses capillaires pourrait résulter d'un étirement mécanique de la membrane basale altérant les propriétés de selectivité par rapport à la taille du filtre glomérulaire lors de l'hypertension aiguë; *(3)* la surface réduite des pores des slit-diaphragmes de filtration implique une moindre conductance hydraulique du filtre glomérulaire qui pourrait être responsable de la diminution du coefficient d'ultrafiltration capillaire glomérulaire présent dans ce modèle d'hypertension.

Acute hypertension induced by angiotensin II (AII) administration reduces glomerular plasma flow and raises glomerular intracapillary pressure [1–5]. Glomerular filtration rate (GFR) remains constant or decreases because of the lowering action of AII on the glomerular ultrafiltration coefficient, Kf [2, 4–6]. Kf is the product of two factors: the aggregate capillary surface in the glomerulus and the hydraulic permeability of the capillary wall [6]. A reduced Kf may be attributed to the "contraction" or "collapse" of glomerular capillary loops [7, 8], a condition that implies a decrease in the surface area of capillary available for ultrafiltration [2, 5, 6]. Alternatively, a reduction in length of the filtration slit diaphragms may decrease the hydraulic conductivity of the filter by limiting the transglomerular passage of water and solutes [9, 10]. AII-provoked hypertension is also associated with a greater glomerular permeability to proteins [11–15] and accumulation of albumin and IgG in the mesangium of subcapsular renal corpuscles (RC) [14]. The hemodynamic alterations indicated above may account for the glomerular leakage of proteins, although a defect in the glomerular filter cannot be excluded [3, 11–15].

In this study the changes in the surface area of the capillary wall and in the length of slit diaphragms have been measured morphometrically in subcapsular RC following the infusion of pressor doses of AII. These morphological evaluations have been correlated with the quantitative and qualitative analysis of urinary protein excretion. Finally, the alterations in the component volumes of epithelial, endothelial, and mesangial cells have been measured to characterize the acute adaptive response of the glomerulus in this animal model. The results demonstrate that AII-induced hypertension affects both capillary size and filtration slit diaphragms, suggesting that mechanical stretching of the glomerular filter may contribute to the genesis of proteinuria in this animal model.

Methods

Twelve adult male Munich-Wistar rats (Simonsen Laboratories, Gilroy, California, USA) were used; they weighed between 198 and 265 g and had free access to water and to a standard rat pellet diet. The animals were anesthetized with sodium pentobarbital (Nembutal, Abbott Laboratories, North

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Table 1. Effects of AII infusion on blood pressure and proteinuria[a]

	Hypertensive	Control	Percent difference
Number of rats	6	6	
Body weight, *g*	223 ± 17	228 ± 19	−2
Equilibration period			
Arterial pressure, *mm Hg*	123 ± 10	119 ± 11	3
Proteinuria, *μg/min*			
Left kidney	13.8 ± 4.6	14.0 ± 4.7	−1
Right kidney	15.4 ± 4.3	13.8 ± 2.7	12
AII administration			
Arterial pressure, *mm Hg*	168 ± 7	122 ± 15	38[b]
Proteinuria, *μg/min*			
Left kidney	228 ± 49	18.3 ± 5.4	1146[b]
Right kidney	280 ± 127	18.2 ± 5.9	1438[b]

[a] The values represent means ± SD.
[b] The value represents the percent change that is statistically significant at least at $P < 0.05$.

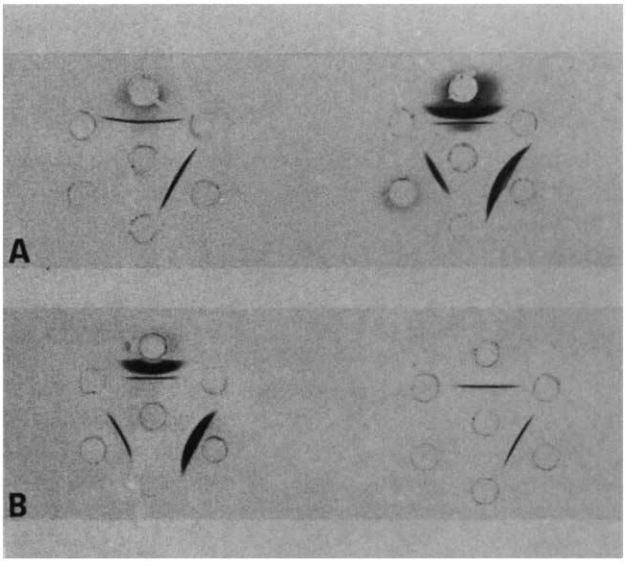


Fig. 1. *Double immunodiffusion reactions between unconcentrated urine* (center wells) *and antisera to rat serum proteins (wells at 12 o'clock), albumin (wells at 4 o'clock), and IgG (wells at 8 o'clock).* The center wells of slide **A** are filled with urine from the left ureter of the same animal before (*left*) and during AII infusion (*right*). In comparison with the control period, the urine contains larger amounts of serum proteins including albumin and IgG during hypertension. Slide **B** compares the urine from two different animals [hypertensive (*left*) and normotensive (*right*)], collected during the second period of infusions.

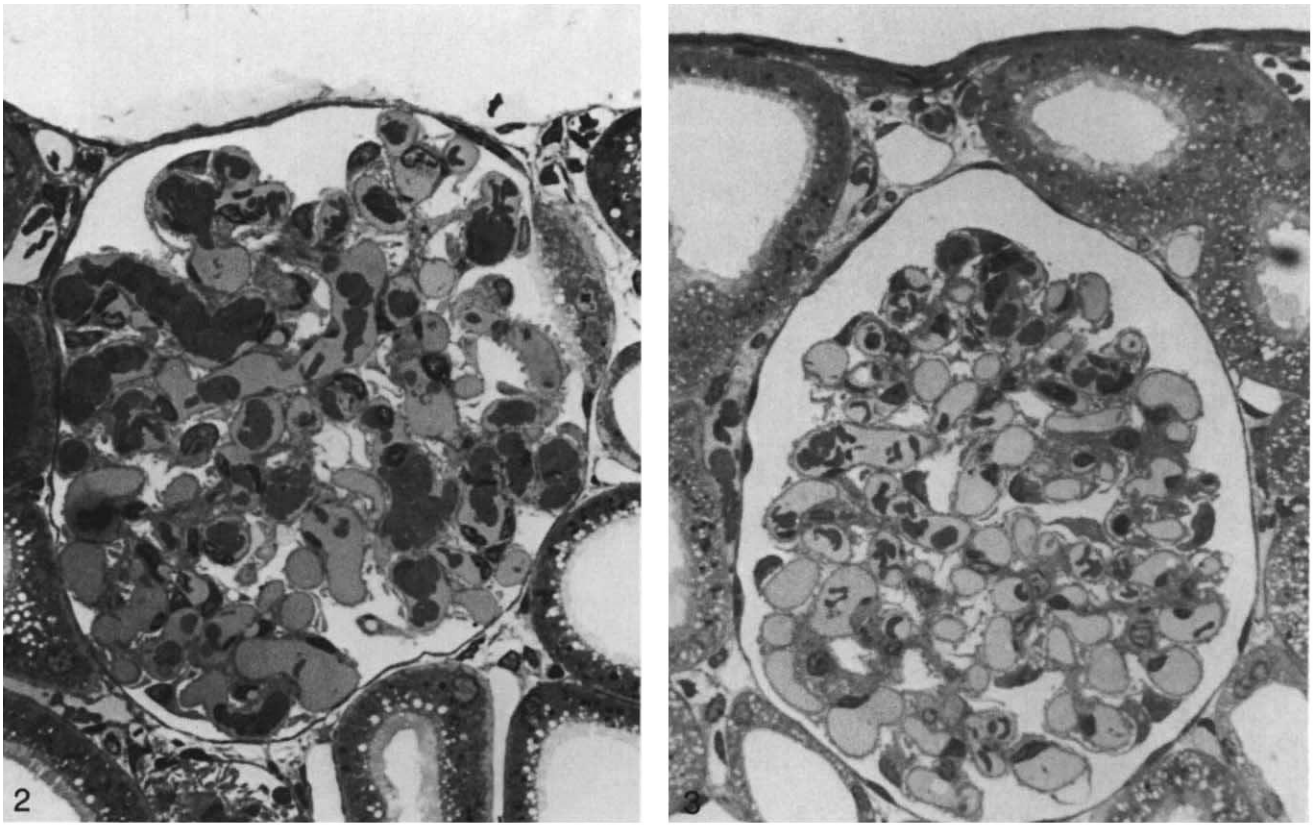
Chicago, Illinois, USA), 4.5 mg/100 g body weight, injected into the tail vein; maintenance doses were given as required. Following tracheostomy, polyethylene catheters (PE 50, Clay Adams, Parsipanny, New Jersey, USA) were inserted into the right femoral vein for intravenous infusions, left carotid artery for blood pressure measurements, and both ureters to collect urine separately from each kidney. After an equilibration period of saline infusion (0.31 ml/100 g/hr) for 30 to 60 min depending on the urinary flow, six rats were subjected to 1 hr infusions of synthetic angiotensin amide (Hypertensin, Ciba Pharmaceutical Company, Summit, New Jersey, USA) dissolved in saline at a constant rate of 1.7 μg/min/kg as previously described [14]. Six animals served as controls and were infused with the same volume of saline for the same period of time. Arterial blood pressure was constantly monitored with a fluid transducer (Sanborn 267 AC) connected to a recording oscillograph (Hewlett-Packard, Elkhart, Indiana, USA). Urine was separately collected in both equilibration and experimental periods in preweighed micro test tubes, and the volume was determined gravimetrically.

At the end of infusions the left kidney was exposed and fixed in situ by dripping a solution of 2% glutaraldehyde in 0.1 M phosphate buffer (pH 7.3) for 45 min on the ventral surface. The accumulation of fixative in the abdomen was prevented by continuous aspiration. The kidney was then excised and the fixed cortex cut into approximately 16 to 20 strips, 0.5 to 1 mm thick, perpendicular to the long axis. The specimens were kept in fresh fixative for an additional 3 hr, washed in the same buffer, and stored overnight at 4°C. They were postfixed in phosphate buffered 1% osmium tetroxide, dehydrated with acetone, and flat-embedded in araldite.

Sections containing the full thickness of the cortex were cut at 0.5 μm with an ultramicrotome (MT-1 Sorvall, DuPont Instruments, Newtown, Connecticut, USA) and stained with methylene blue and safranin. Ultrathin sections were cut with a diamond knife, stained with uranyl acetate and lead citrate, and examined in an electron microscope (Philips EM 400).

As a result of this procedure a layer 200 to 300 μm thick of superficial renal cortical tissue was adequately fixed [16], and only the RC (subcapsular RC) fully contained in this outer portion of the cortex were analyzed. By serial sectioning the embedded slices, a minimum of 12 and a maximum of 18 RC in each animal were found and their profiles photographed and printed at a calibrated magnification of ×1,250. The micrographs collected from each individual RC were evaluated with an interacting tracing device (Videoplan, Carl Zeiss, Oberochen, Germany) to determine the maximum diameter and corresponding volume for that particular RC. A total of 162 pictures, each representing a mid-section of subcapsular RC profiles, 77 from the AII-infused animals and 85 from the control rats, were selected. This sampling was used to compute the average RC diameter and volume in each animal. These values were then used to estimate the mean and standard deviation (SD) of RC diameter and volume in each of the two groups of animals studied. Because of the small number of subcapsular RC present in the renal cortex of Munich-Wistar rats and the impossibility of obtaining an adequate random sampling of RC profiles, the methodology previously utilized in other laboratories [9, 17] could not be applied here.

The capillary numerical density (number of capillary profiles per unit area of glomerular tuft) and the partial volumes occupied by Bowman's space and glomerular tuft in the RC were measured in each of the 162 micrographs. The latter measurement was derived by superimposing on the pictures a 180 × 150-mm morphometric grid consisting of 270 sampling points. The number of points overlying the urinary space located outside the external contour of the glomerular tuft was counted and considered as Bowman's space, while the number of points touching the glomerular tuft inclusive of the entrapped



Figs. 2 and 3. *Light micrographs of representative cross sections of superficial renal corpuscles less than 200 μm below the renal surface, from hypertensive* (Fig. 2) *and normotensive* (Fig. 3) *animals.* After AII infusion the glomerular tuft occupies a larger portion of Bowman's space and exhibits prominent dilation of the capillary loops that may contain numerous red blood cells. (Stained with methylene blue and safranin, ×220)

urinary space was recorded as the glomerular tuft volume fraction.

Six RC from each rat were thin sectioned for quantitative electron microscopic analysis. A total of 360 micrographs, five from each glomerular tuft, 30 from each animal, were printed at ×8,255 as calibrated with a diffraction grating replica (2,157 lines/mm, Pelco, Tustin, California, USA) and analyzed with a 160 × 255-mm morphometric grid containing 352 sampling points and 22 line segments each 160 mm in length. The volume fractions of glomerular tuft components were measured by counting the points overlying Bowman's space inside the glomerular tuft; epithelial, endothelial, and mesangial cells; and capillary lumen, basement membrane, and mesangial extracellular space (ECS). In a previous investigation in the same animal model immunoenzymatic techniques at the electron microscopic level were used to identify the large amount of proteins deposited between the cytoplasmic projections of the mesangial cells and the mesangial matrix [14]. In the present study ECS includes the mesangial matrix and the proteinaceous material accumulated in the mesangial region. The boundaries between these two components are indistinguishable by standard electron microscopic preparations, thus precluding a separate quantitative evaluation. Counts were recorded for points overlying the lamina fenestrata of the endothelial cells and foot processes of the podocytes. We considered as foot processes all the cytoplasmic projections from the primary, secondary, and tertiary trabeculae of the podocytes coming in contact with the basement membrane.

The surface density of glomerular basement membrane (surface area per unit glomerular volume) was measured by the frequency of profile intersections with the sampling line [18, 19]. The numerical density of slit diaphragms that is proportional to their length per unit volume, was obtained by counting the number of filtration slit diaphragms per unit area of glomerulus. This figure multiplied by two gives the length of slit diaphragms per unit of glomerular volume [9]. The mean cross-sectional area of the glomerular capillaries was determined by dividing their luminal volume measured at the electron microscopic level by their length [20, 21]. Capillary length was derived from their numerical density in the glomerular tuft determined by high power light microscopic morphometry (see above) and the reference volume was corrected for the fraction of Bowman's space entrapped inside the glomerular tuft [21]. The absolute volume, surface, and length of the different glomerular constituents were determined from the product of their relative values and the mean glomerular volume in each animal. The effect of compression artifact occurring during microtomy was estimated and found to be 0.94 and 0.93 for thick and thin sections, respectively [21]. The measured values were all corrected as previously described [21].

The protein content in the ureteral samples was quantitatively evaluated with the method of Lowry et al [22] after trichloroacetic acid precipitation. In addition, each sample was

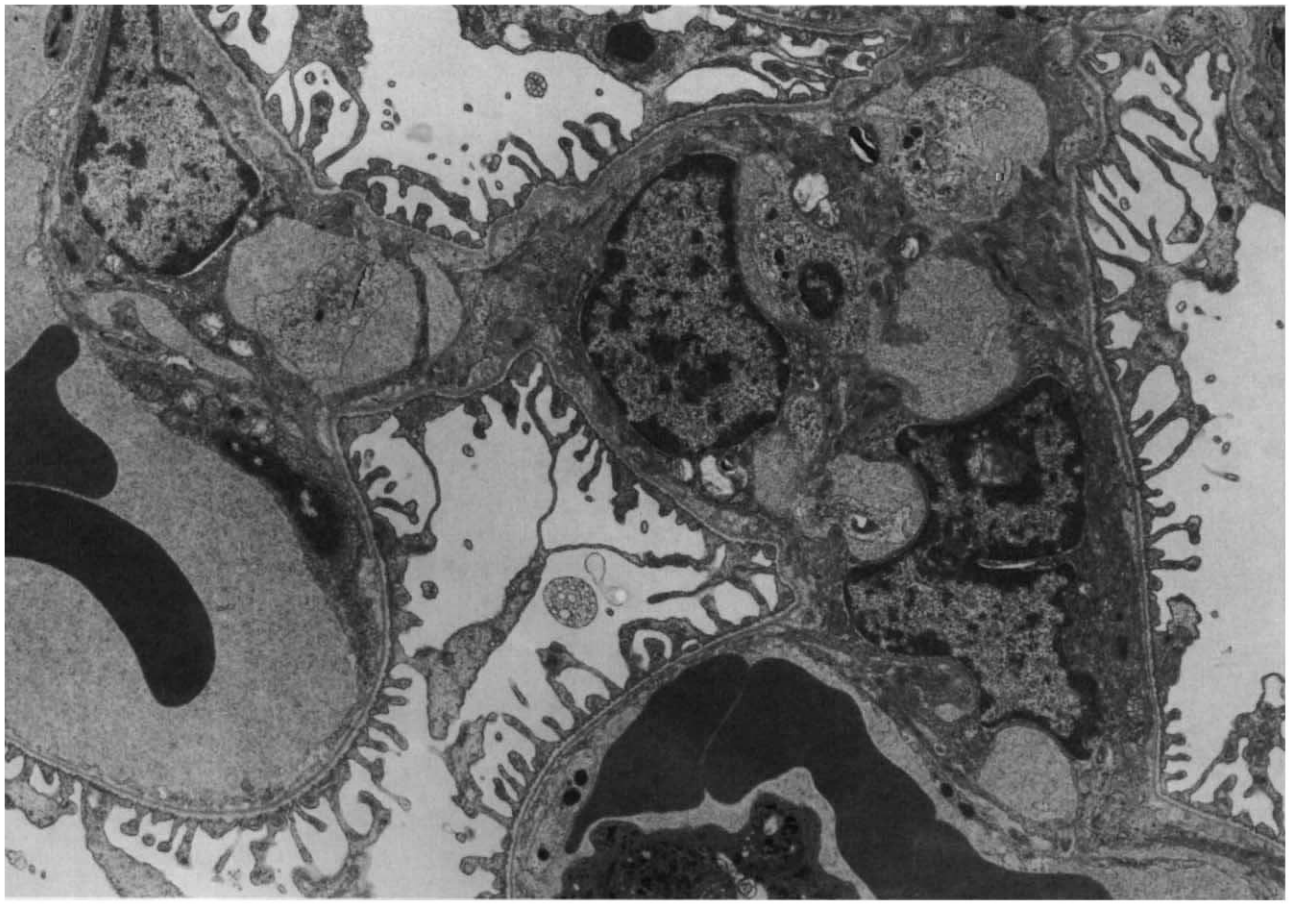


Fig. 4. *Electron micrograph of the mesangium after AII infusion.* The cytoplasm of the mesangial cells is reduced and characterized by slender processes that surround expanded extracellular spaces. No appreciable morphologic alteration in the foot processes can be seen. (Stained with uranyl acetate and lead citrate, ×8,100)

analyzed with agar gel electrophoresis, immunoelectrophoresis, and double immunodiffusion (Ouchterlony) using polyvalent antisera to rat serum proteins and monospecific antisera to rat albumin and IgG (Cappel Laboratories, Cochranville, Pennsylvania, USA). All the results in each table show the mean ± SD of values determined for the individual animal in each group. The statistical significance of differences between the results was determined by Student's t test.

Results

Body weight, systolic blood pressure, and proteinuria of AII-infused rats and control animals are shown in Table 1. Arterial blood pressure in AII-infused rats shows a mean elevation of 45 mm Hg from baseline values, corresponding to a 38% increase over that of the controls ($P < 0.0001$). The rate of urinary protein excretion measured prior to AII infusion is similar in both groups of animals (left kidney $P < 0.95$, right kidney $P < 0.5$). With AII the average amount of proteins in the ureteral samples increases 12- and 15-fold, respectively, in the left ($P < 0.0001$) and right kidney ($P < 0.001$). The unconcentrated urine samples contain small amounts of albumin during the equilibration period in both rat groups (Fig. 1). The major component of AII-induced proteinuria is serum albumin but other proteins were also present, including substantial quantities of IgG. Albumin and IgG in the urine form a single precipitin line when tested by double immunodiffusion using appropriate monospecific antisera (Fig. 1).

The superficial RC of both rat groups are well preserved, as evidenced by distended capillary loops and easily recognizable cellular components (Figs. 2 and 3). No pathologic changes are found by light microscopy in the RC of AII-infused rats. However, their capillary lumina contain a larger number of red blood cells and the glomerular tufts occupy a greater fraction of the urinary space in comparison with that of controls (Figs. 2 and 3). By electron microscopy the glomerular tuft of AII-infused animals is characterized by capillary lumina filled with red blood cells and proteinaceous material, by intact endothelial cells, and by podocytes containing a large number of dense bodies, but without evident modifications in foot process organization. The mesangial cells are surrounded by a conspicuous amount of electron dense material that is difficult to distinguish from the mesangial matrix (Figs. 4 and 5).

The effects of AII-induced hypertension on the structural constituents of the superficial RC are summarized in Tables 2 and 3. Hypertension does not significantly change the estimated volumes of superficial RC in comparison with control values ($P < 0.3$, Table 2). The relative and absolute volumes of the

Table 2. Effects of AII administration on the volumes of subcapsular renal corpuscle constituents

	Hypertensive	Control	Percent difference
RC volumes, $\mu m^3 \times 10^{-3}$	1195 ± 131	1093 ± 143	9
Volume percentage of			
BS outside glomerular tuft	14.4 ± 3.1	17.3 ± 2.5	−17
BS inside glomerular tuft	9.5 ± 3.1	12.1 ± 2.7	−21
Glomerular tuft	76.1 ± 4.7	70.7 ± 3.8	8
Volume of BS, $\mu m^3 \times 10^{-3}$	286 ± 64	321 ± 73	−11
Volume of glomerular tuft, $\mu m^3 \times 10^{-3}$	909 ± 115	772 ± 109	18

Abbreviation: BS, Bowman's space. See footnotes to Table 1.

Table 3. Effects of AII administration on the relative composition of glomerular tuft constituents[a]

	Hypertensive	Control	Percent difference
Volume percentage of			
Epithelium	29.6 ± 1.8	30.8 ± 1.1	−4
Nucleus	6.3 ± 0.82	5.8 ± 0.83	9
Cytoplasm	59.1 ± 1.9	61.7 ± 0.92	−4[b]
Foot processes	34.7 ± 2.1	32.5 ± 1.4	7
Basement membrane	4.2 ± 0.68	4.9 ± 0.51	−14
Endothelium	10.6 ± 1.3	11.9 ± 0.96	−11
Nucleus	35.2 ± 2.8	32.2 ± 1.5	9
Cytoplasm	39.8 ± 2.9	46.1 ± 2.9	−14[b]
Lamina fenestrata	24.9 ± 3.5	21.8 ± 3.1	14
Capillary lumen	39.3 ± 2.2	34.8 ± 1.6	13[b]
Mesangium	16.3 ± 1.1	17.6 ± 0.98	−7
Cells	11.4 ± 1.4	14.4 ± 1.1	−21[b]
Nucleus	28.8 ± 2.5	25.2 ± 2.1	14[b]
Cytoplasm	71.2 ± 2.5	74.8 ± 2.1	−5[b]
Extracellular space	4.9 ± 0.97	3.2 ± 0.48	53[b]

[a] The values represent means ± SD.
[b] The value represents the percentage change that is statistically significant at least at $P < 0.05$.

Table 4. Effects of AII administration on the absolute volumes of glomerular cells and mesangium ($\mu m^3 \times 10^{-3}$)[a]

	Hypertensive	Control	Percent difference
Epithelial cells	269 ± 38	238 ± 34	13
Nucleus	17 ± 3	14 ± 3	21
Cytoplasm	159 ± 23	147 ± 21	8
Foot processes	94 ± 14	77 ± 11	22
Endothelial cells	96 ± 17	92 ± 13	4
Nucleus	34 ± 6	30 ± 4	13
Cytoplasm	38 ± 7	42 ± 7	−10
Lamina fenestrata	24 ± 5	20 ± 4	20
Mesangium	148 ± 21	136 ± 19	9
Cells	104 ± 16	111 ± 16	−6
Nucleus	30 ± 5	28 ± 5	7
Cytoplasm	74 ± 11	83 ± 12	−11
Extracellular space	44 ± 8	25 ± 5	76[b]

[a] The values represent means ± SD.
[b] The value represents the percent change that is statistically significant at least at $P < 0.05$.

glomerular tuft and urinary space demonstrate small, insignificant variations (Table 2).

The volume fractions of the different glomerular constituents are shown in Table 3. The largest glomerular component, that is, the capillary lumen, increases significantly ($P < 0.005$) during hypertension. An additional and even larger effect of hypertension is the expansion of the mesangial ECS ($P < 0.01$) that is accompanied by a significant reduction of the adjacent mesangial cell fraction ($P < 0.005$). No significant changes are seen in the other glomerular structural components (Table 3).

When multiplied by the mean glomerular volumes (Table 2), the relative glomerular compositions (Table 3) are translated into the absolute quantities per glomerulus listed in Table 4. The absolute volume of epithelial cells, endothelial cells and mesangium with their respective subdivisions is unaffected by AII treatment, whereas the extracellular material in the mesangium is significantly increased ($P < 0.005$). The effects of AII administration on the glomerular capillary characteristics are listed in Table 5. Hypertension markedly increases capillary luminal volume (33%, $P < 0.01$) by inducing a significant dilatation of the capillaries as demonstrated by the 24% increase in capillary mean cross-sectional area ($P < 0.01$), with only a minor change in the aggregate length of the capillary network (8%, $P < 0.2$). The larger capillary luminal volume, however, does not alter the absolute surface area of the basement membrane (Table 5). In contrast, the total length of the filtration slit diaphragms is significantly reduced after AII administration, (−24%, $P < 0.05$, Table 5).

Discussion

The present study indicates that acute hypertension induced by AII administration significantly increases urinary protein excretion and affects subcapsular RC components by enlarging the average capillary cross-sectional area, by decreasing the length of the filtration slit diaphragms, and by altering the amount of extracellular material present in the mesangium. These changes have been detected in subcapsular RC that were fixed in situ by dripping fixative on the kidney surface in vivo without interference with blood supply, during a period of time in which AII was continously infused and arterial blood pressure monitored. Thus, they should represent the morphologic counterpart of the effects of the vasoactive agent on the RC,

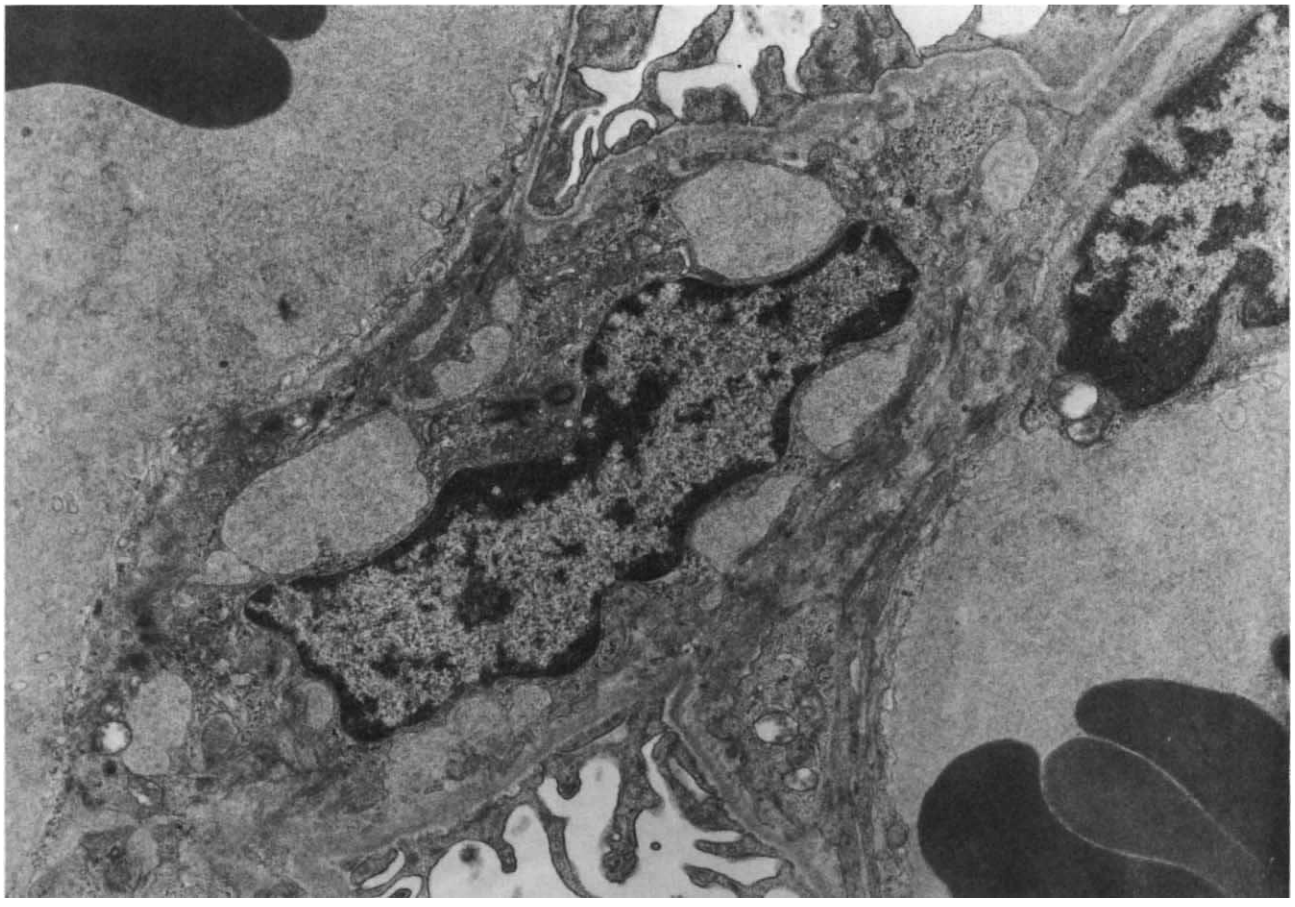


Fig. 5. *Electron micrograph of a mesangial cell with an irregular nuclear profile.* Note the electron opacity of the dilated extracellular space. (Stained with uranyl acetate and lead citrate, ×21,000)

Table 5. Effects of AII administration on the average capillary characteristics[a]

	Hypertensive	Control	Percent difference
Capillary			
Luminal volume, $\mu m^3 \times 10^{-3}$	358 ± 49	269 ± 38	33[b]
Cross-sectional area, μm^2	29.1 ± 2.9	23.5 ± 2.6	24[b]
Length density, mm^2/mm^3	13.6 ± 1.1	14.8 ± 1.4	−8
Length, *mm*	12.32 ± 1.85	11.39 ± 1.95	8
Basement membrane			
Volume, $\mu m^3 \times 10^{-3}$	38 ± 8	38 ± 5	0
Surface density, mm^2/mm^3	291 ± 16	303 ± 17	−4
Surface area, mm^2	0.265 ± 0.037	0.234 ± 0.036	13
Slit diaphragm			
Length density, m/mm^3	689 ± 78	1064 ± 113	−35[b]
Length, *mm*	627 ± 107	822 ± 146	−24[b]

[a] The values represent means ± SD.
[b] The value represents the percent change that is statistically significant at least at $P < 0.05$.

either as a direct influence and/or as a result of its pressor action.

The mechanism by which AII-induced hypertension significantly increases the luminal volume of glomerular capillary loops seems to depend on the action of the peptide on the renal cortical microcirculation. Infusion of pressor and subpressor amounts of AII, either intravenously [1–6] or directly into the renal artery [4], leads to a reduction of glomerular plasma flow with a pronounced rise in glomerular intracapillary pressure [1–6]. Thus, the dilatation of glomerular capillaries as well as the large number of red blood cells trapped in their lumina found here, may result from a combination of the reduction in

glomerular blood flow and the increased intracapillary pressure. In addition, the morphological findings are compatible with evidence that AII affects glomerular hemodynamics by increasing the prevalent resistances of glomerular efferent arterioles [1, 2, 4, 6, 23].

The defective glomerular permeability in this model of hypertension has been attributed to AII-induced renal hemodynamic perturbations [3, 6]. AII enhances the driving forces for diffusion of macromolecules across the glomerular filter by reducing glomerular plasma flow [3]. Thus, the clearance of molecules of the size of albumin may increase without changes in the permeability properties of the capillary wall [3, 6]. Based on the recently described theoretical model for glomerular filtration of macromolecules, a twofold increase in the glomerular filtration of albumin may be expected after AII administration [24]. However, the amount of proteinuria found in the present study largely exceeds the anticipated value. Furthermore, the significant glomerular leakage of IgG molecules (molecular weight, 150,000) cannot be explained by hemodynamic factors alone, but rather seems to imply a defect in the size-selective properties of the glomerular barrier to proteins. This hypothesis is also supported by the absence of defects in the fixed anionic charges in the capillary wall and by the altered glomerular permeability to native ferritin (molecular weight, 500,000) following AII-induced hypertension [15]. The dilatation of the capillary loops observed here may exert a stretching action on the glomerular basement membrane resulting in a larger pore size, with defective sieving characteristics of the filter.

Despite the hemodynamic alterations, GFR in the subcapsular RC is practically unchanged by AII infusion [1, 2, 6]. The maintenance of a nearly constant GFR has been attributed to a significant reduction of the ultrafiltration coefficient, Kf [2, 4, 5]. Since Kf is the product of the capillary surface area and the hydraulic conductivity of the glomerular filter [6], a decreased surface area of the glomerular capillary available for ultrafiltration has been postulated to account for the fall in Kf [2, 4]. In the present investigation, however, the total surface area of glomerular basement membrane was increased 13%, but this change was not statistically significant. The hydraulic conductivity of the glomerular capillary wall to water and solutes is at least in part controlled by the complex structural organization of the slit diaphragms distributed between adjacent foot processes [9, 25, 26]. The observation of a significant reduction of the total length of the filtration slits, if the dimensions of their porous substructure remains constant, suggests a corresponding decrease in their total pore area in hypertension. Although caution should be taken in attempting to correlate morphological findings with functional changes, the present results seem to suggest that the underlying defect in Kf reduction depends on the low hydraulic conductivity of the glomerular filter. This alteration appears to result from the smaller pore area for filtration of the slit diaphragms. Whether this alteration is a direct effect of AII-induced hypertension, or it follows glomerular capillary dilatation or food process swelling in the presence of proteinuria, remains to be determined. A reduction in the length of slit diaphragms can be expected in other glomerular diseases where foot processes are fused and proteinuria occurs [27–29]. These structural and functional glomerular lesions have been found to be associated with a marked reduction of Kf [30].

The quantitation of the mesangial lesions produced by AII administration together with previous observations on glomerular permeability [14], provide evidence that hypertension affects the mesangium, leading to expansion of the extracellular space. The rearrangement of the mesangium can be achieved by the greater pressure gradient at the interface between capillary lumen and the endothelial/mesangial components, resulting in an increased passage and accumulation of proteins. Mesangial cell contraction may also be responsible for the development of such lesions because these cells possess AII receptors [31] and are able to contract in response to vasoactive agents in vitro [32]. Both mechanisms acting synergistically may contribute to the development of the mesangial damage.

In conclusion, the present study demonstrates that acute (AII-induced) hypertension is characterized by the absence of qualitative structural changes in the glomerular capillary network. However, on a quantitative basis significant alterations occur in both the size of glomerular capillaries and the length of slit diaphragms. These morphometric results may explain, at least partially, the defective ability of the glomerular filter to restrict the passage of proteins and the decreased hydraulic conductivity of the capillary wall in hypertension.

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